PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231,
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 July 2000 (18.07.00)	
International application No. PCT/EP99/09053	**Applicant's or agent's file reference** 0/98414 WO
International filing date (day/month/year) 18 November 1999 (18.11.99)	**Priority date** (day/month/year) 20 November 1998 (20.11.98)
Applicant LOOZEN, Hubert, Jan, Jozef et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 June 2000 (15.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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REC'D 14 NOV 2000
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
0/98414 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/09053	18/11/1999	20/11/1998
International Patent Classification (IPC) or national classification and IPC C07J1/00		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/06/2000	10.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rudolf, M Telephone No. +49 89 2399 8604

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09053

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

2-14,14a,15,16	as originally filed			
1	as received on	29/09/2000	with letter of	29/09/2000

Claims, No.:

1-6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-6
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-6
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-6
	No:	Claims

2. Citations and explanations
   see separate sheet

To section V:

The following prior art documents have been cited in the search report:

D1: C. LOBACCARO ET AL: 'Steroidal Affinity Labels of the Estrogen Receptor. 3. Estradiol 11.beta.-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Anti-estrogenic and Cytotoxic Properties' JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 14, 4 July 1997 (1997-07-04), pages 2217-2227, XP002100729 WASHINGTON US

D2: E. NAPOLITANO ET AL: '11.beta.-Substituted Estradiol Derivatives. 2. Potential Carbon-11-and Iodine-Labeled Probes for the Estrogen Receptor' JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 14, 7 July 1995 (1995-07-07), pages 2774-2779, XP002100730 WASHINGTON US cited in the application

D3: DE 41 32 182 A (SCHERING AG) 25 March 1993 (1993-03-25)

D4: WO 93 13123 A (ROUSSEL UCLAF) 8 July 1993 (1993-07-08)

D1 discloses steroid compounds which are substituted at position 11 with hydrocarbon groups having linear chain lengths of 2, 4, and 10 carbon atoms and additionally bearing functional groups. D1 teaches that the receptor affinity increases when the ethylene chain was changed to the n-butylene chain (page 2219, right-hand col.). D2 discloses steroids compounds having a substituent with a linear carbon chain length of up to 3 carbon atoms. D3 discloses steroid compounds bearing a pentafluorosulfinylnonyl group (i.e. a 9-carbon atoms chain) at the coresponding position (cf. compound 4e). The steroid skeleton of this compound is however bridged between C14 and C17, thus said compound does not correspond to formula (I) as claimed.

In contrast to the compounds described in D1 and D2, the present claims are directed to steroids of formula (I) bearing at position 11 a linear carbon chain from 5-9 carbon atoms. Such compounds are not disclosed in the prior art, therefore the claimed subject matter is novel.

The applicant demonstrated in comparative tests that compounds with a hydrocarbon group with a chain length of 5 carbon atoms or more at position 11 of the steroid ring

exhibit a more differentiated receptor affinity (agonist for ERα, antagonist for ERß) compared with compounds which bear a chain of four carbons or shorter at position 11 and which are agonists for both ERα and ERß (cf. table on page 14 of the description). Such differentiated activity of the claimed compounds is not derivable from the cited prior art, the presence of an inventive step therefore can be acknowledged.

ESTROGENIC ESTRA-1,3,5(10)-TRIENES WITH DIFFERENTIAL EFFECTS ON THE ALPHA AND BETA ESTROGEN RECEPTORS, HAVING A LINEAR HYDROCARBON CHAIN OF FROM 5-9 CARBON ATOMS IN POSITION 11

The invention is in the field of estrogenic compounds of the type based on the molecular structure of estradiol. I.e., compounds having a steroidal skeleton the A-ring of which is aromatic, and having a free or capped hydroxyl group at carbon atom No. 3 and at either of carbon atoms Nos. 16 or 17. Estrogenic compounds have a generally recognised utility in the treatment of estrogen-deficiency related disorders, such as menopausal complaints, osteoporosis, and in contraception.

More precisely, the invention pertains to 11β-substituted estradiol derivatives. Such 11β-substituted estradiol derivatives are known from, *inter alia*, Napolitano et al. in J.Med.Chem. **1995**, *38*, 2774-2779. From this paper, it can be learned that placing a substituent at the 11β-position may improve the binding affinity for the estrogen receptor, provided that said substituent is not too large. E.g., with an ethinyl group at C_{11} the binding increases, whereas with the next higher homolog, 1-propinyl, it is reported that the binding affinity undergoes a marked drop.

The state of the art in the field of estrogen receptor affinity discriminates between two estrogen receptors, denoted ERα and ERβ, see Mosselman et al., FEBS Letters 392 (1996) 49-53 as well as EP -A- 0 798 378. Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress, making it possible to provide a more selective treatment of estrogen-deficiency related disorders, with a lower burden of estrogen-related side-effects.

The present invention is based on the unexpected finding that, despite the above teaching, certain 11β-substituted estradiol derivatives that deviate from those reported by Napolitano et al. possess a surprisingly higher estrogen receptor-affinity. Moreover, the present invention pertains to such 11β-substituted estradiol derivatives

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
0/98414 WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/09053	18/11/1999	20/11/1998
Applicant		
AKZO NOBEL N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] it is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

ESTROGENIC ESTRA-1,3,5(10)-TRIENES WITH DIFFERENTIAL EFFECTS ON THE ALPHA AND BETA ESTROGEN RECEPTORS, HAVING A LINEAR HYDROCARBON CHAIN OF FROM 5-9 CARBON ATOMS IN POSITION 11

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]P 99/09053

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J1/00 A61K31/565 C07J21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C. LOBACCARO ET AL: "Steroidal Affinity Labels of the Estrogen Receptor. 3. Estradiol 11.beta.-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Anti-estrogenic and Cytotoxic Properties" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 14, 4 July 1997 (1997-07-04), pages 2217-2227, XP002100729 WASHINGTON US * page 2218, compound 5b * page 2219; table 1 page 2221; table 2 --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2000	10/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]EP 99/09053

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. NAPOLITANO ET AL: "11.beta.-Substituted Estradiol Derivatives. 2. Potential Carbon-11-and Iodine-Labeled Probes for the Estrogen Receptor" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 14, 7 July 1995 (1995-07-07), pages 2774-2779, XP002100730 WASHINGTON US cited in the application page 2776; table 1 ---	1-6
A	DE 41 32 182 A (SCHERING AG) 25 March 1993 (1993-03-25) the whole document ---	1-6
A	WO 93 13123 A (ROUSSEL UCLAF) 8 July 1993 (1993-07-08) * the whole document, in particular, page 17, paragraph 3-4 * -----	1-6

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